DETAILED ACTION

Status of the claims

The amendment filed January 19, 2010 is acknowledged and has been entered. Currently, claims 1-29, 31, 34, 36-39 and 41-65 are pending. Claims 1-26, 34, 37 and 41-65 are withdrawn as being directed to non-elected inventions. Claims 27-29, 31, 36, 38 and 39 are under examination.

Withdrawn Rejections

All rejections of claims not reiterated herein, have been withdrawn.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 27, 28 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lollar (US 2005/0079584) in view of Ritter et al., (US 2003/0040027).

Lollar discloses a method for determining if a patient comprises inhibitory antibodies (autoantibodies) (e.g. para. 0007, para. 0114) to hybrid factor VIII (natural substance). Lollar discloses treating the patient with factor VIII (para. 0114). Lollar discloses obtaining sample from the patient and assessing the sample for the quantity (para. 0038 of the antibodies (para. 0114). Lollar discloses that antibodies can be detected with an ELISA or radioimmunoassay (para. 0134). Lollar discloses that the factor VIII can be used in the method when the factor VIII contains at least one antigenic site (unhindered) and wherein the amount is sufficient for form a detectable complex with the inhibitory antibodies in the sample (para. 0134). Lollar also discloses that the amount of the antibody in the test sample can be used to assist in the selection of medical therapies (para. 0038).

Lollar differs from the instant invention in failing to teach altering the level or concentration of said therapeutic administration of the natural substance to the subject.

Ritter et al disclose methods of determining immune reactive molecules such as antibodies against therapeutic agents administered to subject (e.g. abstract, para 0018, 0043). Ritter et al disclose determining the quantity of the reactants in the subjects sample (e.g. para. 0043) and discontinuing (altering) the therapeutic regime based on this determination (e.g. para 0021, 0042, 0043).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to discontinue administration of therapeutic reagents such as

taught in Lollar because Ritter et al teaches that it is known in the art of therapeutics to discontinue administration of therapeutic agents which cause the production of immune reactive molecules in a subject. Further, it is well within the realm of one of ordinary skill in the art to alter the level or concentration of a therapeutic agent to a subject when the subject is developing immune reactive molecules to the administered agent.

4. Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Conti-Fine (US 6,759,385) in view of Lollar (US 2005/0079584) and further in view of Ritter et al., (US 2003/0040027).

Conti-Fine discloses methods of detecting antibodies specific for endogenous antigen. Conti-Fine discloses the administration of endogenous protein (natural substance) or derivatives of the protein (analogs) to a subject (col 6, line 61 – col 7, line 30). Conti-Fine discloses assessing antibodies produced as a result of the administration of the protein or its derivative (analog)(col 2, lines 19-30, col 24, lines 12-26, col 90, lines 15-20, col 91, lines 30-37). Conti-Fine discloses making decisions on therapeutic administration (col 7, lines 43-52).

Conti-Fine differs from the instant invention in failing to specifically teach the auto antibody is not assessed via plasmon resonance.

Lollar discloses a method for determining if a patient comprises inhibitory antibodies (autoantibodies) (e.g. para. 0007, para. 0114) to hybrid factor VIII (natural substance). Lollar discloses treating the patient with factor VIII (para. 0114). Lollar discloses obtaining sample from the patient and assessing the sample for the presence

of the antibodies (para. 0114). Lollar discloses that antibodies can be detected with an ELISA or radioimmunoassay (para. 0134). Lollar discloses that the factor VIII can be used in the method when the factor VIII contains at least one antigenic site (unhindered) and wherein the amount is sufficient for form a detectable complex with the inhibitory antibodies in the sample (para. 0134).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate ELISA or radioimmunoassays into the method of Conti-Fine because Conti-Fine specifically teaches that the endogenous protein administered can be factor VIII and Conti-fine is generic with respect to how the antibodies are detected and Lollar teaches that it is known in the art to utilize assays such as ELISA or radioimmunoassays to detect antibodies which are developed due to the administration of an endogenous protein.

Conti-Fine and Lollar differ from the instant invention in failing to teach altering level or concentration of said therapeutic administration of the natural substance to the subject.

Ritter et al disclose methods of determining immune reactive molecules such as antibodies against therapeutic agents administered to subject (e.g. abstract, para 0018, 0043). Ritter et al disclose determining the quantity of the reactants in the subjects sample (e.g. para. 0043) and discontinuing (altering) the therapeutic regime based on this determination (e.g. para 0021, 0042, 0043).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to discontinue administration of therapeutic reagents such as

taught in the modified method of Conti-Fine because Ritter et al teaches that it is known in the art of therapeutics to discontinue administration of therapeutic agents which cause the production of immune reactive molecules in a subject. Further, it is well within the realm of one of ordinary skill in the art to alter the level or concentration of a therapeutic agent to a subject when the subject is developing immune reactive molecules to the administered agent.

5. Claims 29 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Conti-Fine in view of Lollar and Ritter et al as applied to claims 27 and 28 above, and further in view of Bunn (N. ENGL. J. Med. Vol 346, No. 7, pgs 522-523 2002).

See above for the teachings of Conti-Fine, Lollar and Ritter et al.

Conti-Fine, Lollar and Ritter et al differ from the instant invention in failing to teach the natural substance is erythropoietin or analog epoetin.

Bunn describes a method of deciding to initiate or terminate administration of "erythropoietin" or epoetin (analog of erythropoietin (p. 522, left column, third paragraph, first sentence, "[t]he article by Casadevall et al. in this issue of the Journal") based on an assessed autoantibody (p. 522, left column, third paragraph, second sentence, "immune response to epoietin") against both endogenous erythropoietin and recombinant erythropoietin (p. 522, right column, second paragraph, second sentence, "the antibody must react not only with epoietin but also with the small amount of endogenous erythropoietin").

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the modified method of Conti-Fine et al, to erythropoietin or epoietin because Conti-Fine is generic with respect to the endogenous protein for administration and according to Bunn, "about 3 million patients worldwide are being treated with epoetin" and because "[t]he clinical picture rapidly developing transfusion-dependent anemia is so dramatic that such cases are unlikely to escape attention (p. 522-523).

6. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lollar in view of Ritter et al and further in view of Voller (Diagnostic Horizons, Dynasciences Corporation, Published by Microbiological Associates, Vol. 2, No. 1, pgs 1-7, 1978).

See above for the teachings of Lollar and Ritter et al.

Lollar and Ritter et al differ from the instant invention in failing to teach the autoantibody is assessed by a sandwich assay format.

Voller teaches that it is known in the art of ELISA assays to provide sandwich assay formats to determine a substance such as antibodies in a sample (e.g. p. 2, p. 4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a sandwich assay format into the modified method of Lollar because Lollar specifically teaches that ELISA assay can be used to detect the antibodies and Lollar also teaches that reagents and methods are known to those skilled in the art (para. 0134) and Voller shows that sandwich assay formats are known for the detection of antibodies in a sample.

7. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lollar in view of Ritter et al and further in view of Stevens (Clinical Immunology and Serology, A Laboratory Perspective, Chapter 10, Labeled Immunoassays, pages 144-146, 1996.)

See above for the teachings of Lollar and Ritter et al.

Lollar and Ritter et al differ from the instant invention in failing to teach labeling the natural substance and separating labeled autoantibody complex from the reaction mixture.

Stevens teaches that it is known in the art of immunoassays to label either the ligand or receptor and to provide separation steps to separate reacted complex from unreacted complexes prior to detection of the labeled complexes (pgs 145-146). Stevens teaches that the labels can be radioactive, enzymes and chemiluminescent labels (p. 146) (note same labels as disclosed by Applicant, therefore are low molecular weight labels).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate labels and separation steps such as taught by Stevens into the modified method of Lollar because Lollar specifically teaches that reagents and methods are known to those skilled in the art to detect antibodies in a sample(para. 0134) and Stevens teaches that it is well known in the art of immunoassays to label either the ligand or receptor and to provide separation steps to separate reacted complex from unreacted complexes prior to detection of the labeled complexes.

With respect the recitation "and wherein the proportion of the molecular weight of the low molecular weight label bound to the unhindered natural substance versus the molecular weight of the unhindered natural substance itself, comprises less that about 50%" as recited in the instant claim. Since the combination of Lollar, Ritter et al and Stevens teaches reagents consonant to those instantly claimed. It is deemed the molecular weight of the low molecular weight label that is capable of binding the unhindered natural substance comprises less than about 50%. Further, the optimum proportion of the molecular weight of the low molecular weight label versus the molecular weight of the unhindered natural substance itself can be determined by routine experimentation and thus is considered to be obvious to one of ordinary skill in the art. Also, it has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation ." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272,276, 205 USPQ 215, 218-219 (C.C.P.A. 1980).

Response to Arguments

8. Applicant's arguments filed 01/19/10 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

9. No claims are allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GARY W. COUNTS whose telephone number is (571)272-0817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

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/ Gary W. Counts/

Examiner, Art Unit 1641

/Melanie Yu/
Primary Examiner, Art Unit 1641